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Ambient Water Quality Criteria Document
Addendum for Chloroalkyl Ethers

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ADDENDUM FOR CHLOROALKYL ETHERS

Prepared for

OFFICE OF WATER REGULATIONS
AND STANDARDS

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
PEL	Permissible exposure limit
ppb	Parts per billion
ppm	Parts per million
RFD	Reference dose
RQ	Reportable quantity
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RFD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RFD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RFD = \frac{NOAEL \text{ or } LOAEL}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RFDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in

animals in the absence of human data); Group D - Not Classifiable as to Human Carcinogenicity (Inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on chloroalkyl ethers, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1986 to 1988 for bis(2-chloroethyl)ether and 1980 to 1988 for the other chloroalkyl ethers). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Since the original derivation of ambient water quality criteria for bis(chloromethyl) ether, bis(2-chloroethyl) ether and bis(2-chloro-1-methyl-ethyl) ether [incorrectly called bis(2-chloroisopropyl) ether] (U.S. EPA, 1980), no new data have become available to derive criteria for other chloroalkyl ethers. A few reports have been published for those compounds listed above, however, that could affect the existing criteria.

While bis(chloromethyl) ether still lacks direct data for oral exposure, Leong et al. (1981) reported a three-dose-level lifetime inhalation study, which confirmed a high degree of carcinogenicity of this chemical to rats at 100 ppb. Groups of 120 male SPF Sprague-Dawley rats and 144-157 male Ha/ICR mice were exposed to 0, 1, 10 or 100 ppb (0, 5, 47 or 470 $\mu\text{g}/\text{m}^3$) bis(chloromethyl) ether, 6 hours/day, 5 days/week for 6 months and observed for their lifespan. The formation of benign pulmonary adenomas in mice exposed to 100 ppb bis(chloromethyl) ether provided some evidence of carcinogenicity, but the significance of the tumors was confounded by ascending urinary tract infections that resulted in excessive early mortality in both control and treated mice, and therefore will not be discussed further. In rats, gross necropsies and comprehensive histologic examinations showed a statistically significant ($p \leq 0.05$) incidence of benign nasal esthesioneuroepitheliomas only in the 100 ppb exposure group (0/112 for controls, 0/113 for 1 ppb, 0/111 for 10 ppb and 96/111 for 100 ppb). Four rats in the 100 ppb exposure group also developed pulmonary adenomas. The incidence of these tumors was not statistically significant ($p = 0.059$). A high degree of tumor-related mortality was reported in the 100 ppb exposure group after the 7th month of the experiment. Most of the other rats died of spontaneous or age-related diseases after the 16th month. In comparison, Kuschner et al. (1975)

revealed that in the earlier study, the incidences of malignant respiratory tumors in rats caused by 100 ppb bis(chloromethyl) ether were about equally divided between nasal tumors (esthesioneuroepitheliomas) and bronchogenic squamous cell carcinomas, whereas only the nasal tumors were observed in the study by Leong et al. (1981). Leong et al. (1981) attributed the difference to their use of SPF rats, indicating a possible strain difference in responses to the carcinogenic effects. These authors also showed that the nasal tumor incidence resulting from 129 exposures to 100 ppb bis(chloromethyl) ether was a direct extension of the combined incidence of respiratory tract cancer produced by 10-100 exposures to 100 ppb in the study by Kuschner et al. (1975), when plotted on the exposure-response curve for number of exposures at 100 ppb vs. cancer incidence. In conclusion, the results reported by Leong et al. (1981) are consistent with previous reports where bis(chloromethyl)ether at 100 ppb (in rats) produced an oncogenic response.

Another inhalation study on bis(chloromethyl) ether (Dulak and Snyder, 1980) found development of respiratory tract tumors in ~35% of male Sprague-Dawley rats exposed to 0.1 ppm, 6 hours/day, 5 days/week for 30 exposures and observed for life. Types of tumors and other details were not reported.

U.S. EPA (1987a) reviewed the data base for bis(chloromethyl) ether and concluded that in comparison with the inhalation study by Leong et al. (1981), the earlier work by Kuschner et al. (1975), on which the present ambient water quality criteria for this chemical is based, was less suited for risk assessment because of the use of different exposure lengths rather than actual different exposure levels and the lack of explicit reporting on the control group. Based on dose-response data for nasal esthesioneuroepitheliomas in male rats in the Leong et al. (1981) study, U.S. EPA (1987a) derived a human oral q_1^* of $59.54 \text{ (mg/kg/day)}^{-1}$. U.S. EPA (1987a) also

noted problems in the procedure of criteria derivation used in the AWQCD (U.S. EPA, 1980). The derivation of ambient water standards for bis(chloromethyl)ether is believed to be of academic interest only, since α -chloroalkyl ethers are rapidly hydrolyzed in water. Also, carcinogenicity data for oral administration of these compounds are not available.

The carcinogenicity of 100% pure bis(2-chloroethyl) ether has been evaluated in an oral exposure study (Weisburger et al., 1981). Gavage doses of 25 or 50 mg/kg twice weekly for 78 weeks followed by a 26-week observation period failed to reveal evidence of carcinogenicity in groups of 26 male and 26 female Charles River CD rats, compared with vehicle and untreated controls.

High purity (98.5%) bis(2-chloro-methylethyl) ether was not carcinogenic to groups of 56 male and 56 female SPF ICR mice fed diets containing 0, 80, 400, 2000 or 10,000 ppm of the chemical for ≤ 104 weeks (Mitsumori et al., 1979). At 10,000 ppm a depression of body weight gain corresponding with decreased food consumption was noted in both sexes of mice. In addition, mild anemia and increased extramedullary hematopoiesis of the spleen were observed. At 2000 ppm only female mice experienced depression of body weight gain and anemia. Therefore, Mitsumori et al. (1979) concluded that 2000 ppm (198 mg/kg/day) was a NOEL in male mice and 400 ppm (35.8 mg/kg/day) was a NOEL in female mice.

Technical grade bis(2-chloro-methylethyl) ether of ~70% purity containing ~28.5% 2-chloro-1-methylethyl(2-chloropropyl) ether, however, produced clear evidence of carcinogenicity when tested by gavage in groups of 50 male and 50 female B6C3F1 mice at 0, 100 and 200 mg/kg/day, 5 days/week for 103 weeks, followed by 1-7 weeks of observation (NTP, 1982). Treatment with the

technical grade chemical significantly increased the incidences of hepatocellular carcinomas and adenomas in the male mice (13/50 for controls, 23/50 for 100 mg/kg, 27/50 for 200 mg/kg) (NTP, 1982). In addition, treatment significantly increased the incidences of alveolar/bronchiolar adenomas in both males and females. Squamous cell papillomas of the stomach or forestomach were found in two high-dose females and in one low-dose and one high-dose male; a squamous cell carcinoma of the forestomach was found in a third high-dose female. Although not statistically significant, the occurrence of these tumors was thought to be related to treatment because of their rarity in vehicle and untreated control B6C3F1 mice.

Based on epidemiologic evidence of induction of respiratory cancer in exposed workers and the induction of nasal and lung tumors in rats, mice and hamsters exposed by inhalation (U.S. EPA, 1980), technical grade chloromethyl methyl ether has been given the verified classification of U.S. EPA Group A carcinogen (U.S. EPA, 1987b). Similarly, epidemiologic evidence of lung tumors (oat cell carcinomas) in workers and the induction of respiratory tract tumors in rats and mice (U.S. EPA, 1980) are the basis for the verified classification of bis(chloromethyl) ether in U.S. EPA Group A (U.S. EPA, 1988a).

The above epidemiologic studies generally involved workers exposed to chloromethyl methyl ether contaminated with bis(chloromethyl) ether; the predominant cancer was lung carcinoma of the oat-cell type. Additional epidemiology studies, published after the AWQCD and not evaluated during verification of weight-of-evidence classifications, include those of Collingwood et al. (1987), Maher and DeFonso (1987), Schaffer et al. (1984) and Weiss (1982). Most of these are follow-up studies of cohorts discussed

in the AWQCD (U.S. EPA, 1980), and all involve exposure of workers to chloromethyl methyl ether contaminated with bis(chloromethyl) ether. None of the studies appears to provide dose-response data suitable for quantitative risk assessment. An additional report describes three lung cancer deaths in young men exposed to bis(chloromethyl) ether generated during chloromethylation processes (Roe, 1985).

The induction of hepatomas by orally administered commercial grade bis(2-chloroethyl) ether in two strains of mice and predominantly positive mutagenicity tests are the basis for the verified classification of bis(2-chloroethyl) ether as a Group B2 carcinogen - probable human carcinogen (U.S. EPA, 1986).

Limited experimental evidence for carcinogenicity in oral studies (i.e., the carcinogenicity in mice, but not in rats, of a 70%-pure preparation and the lack of cancer induction by a high-purity material in mice) has led to the classification of bis(2-chloro-1-methylethyl) ether in Group C - possible human carcinogen (U.S. EPA, 1987a).

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for chloroalkyl ethers are currently undergoing Agency review. The BCF of 2.47 for bis(2-chloro-1-methyl-ethyl)ether, 0.63 for bis(chloromethyl) ether and 6.9 for bis(2-chloroethyl)ether from the U.S. EPA (1980) will be used until this review is completed.

QUANTIFICATION OF EFFECTS

No ambient water quality criteria were derived for chloromethyl methyl ether because derivation of an oral criterion was deemed incongruous with the extreme instability of this chemical in aqueous media (half-life <1 second) (U.S. EPA, 1980).

In view of the somewhat longer half-life of bis(chloromethyl) ether, the U.S. EPA (1980) derived criteria for excess cancer risks as a guideline, based on a rat chronic inhalation study (Kuschner et al., 1975). In this study, Sprague-Dawley rats were treated with 0.1 ppm bis(chloromethyl) ether 6 hours/day, 5 days/week for 10-100 exposures, followed by observation for the rest of the lifespan. The incidences of malignant respiratory tumors (primarily nasal neuroepitheliomas and pulmonary squamous cell carcinomas) increased with increasing number of exposures. Following conversion of exposure data to mg/kg/day data for each group, a human carcinogenicity potency factor, q_1^* , of $9299.8 \text{ (mg/kg/day)}^{-1}$ was calculated. Using a BCF of 0.63, ambient water quality criteria for an excess cancer risk of 10^{-5} , 10^{-6} and 10^{-7} were 37.6×10^{-3} , 3.76×10^{-3} and 0.376×10^{-3} ng/l for exposure through consumption of 2 l of drinking water and 6.5 g of fish and shellfish, and 18.4, 1.84 and 0.184 ng/l for exposure through consumption of fish and shellfish only (U.S. EPA, 1980).

The U.S. EPA (1988a) has reevaluated the data for the carcinogenicity of bis(chloromethyl) ether and concluded that although the Kuschner et al. (1975) rat data are an appropriate basis for quantitative risk assessment, the dose conversion in the AWQCD was incorrect. Accordingly, different mg/kg/day doses were calculated and used to derive a human q_1^* (slope factor) of $2.2 \times 10^2 \text{ (mg/kg/day)}^{-1}$. This slope factor has been verified

(U.S. EPA, 1988a). The U.S. EPA (1987a) evaluated the more recent carcinogenicity data for rats provided by the study of Leong et al. (1981) and derived a slope factor of $59.5 \text{ (mg/kg/day)}^{-1}$ based on that data. The Leong et al. (1981) study may also provide a basis for a verified cancer potency estimate (see Review of New Data section); therefore, it is recommended that the verified slope factor be reconsidered.

Using the current verified q_1^* of $2.2 \times 10^2 \text{ (mg/kg/day)}^{-1}$ for bis(chloromethyl) ether, and assuming 70 kg body weight and a daily intake of 2 L of water and 6.5 g of fish and shellfish with a BCF for bis(chloromethyl) ether of 0.63, the criteria for bis(chloromethyl) ether in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/L)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 L of drinking water and consumption of 6.5 g of fish and shellfish	0	0.016	0.16	1.6	16
Consumption of fish and shellfish only	0	7.7	78	780	7800

The U.S. EPA (1980) derived criteria for bis(2-chloroethyl) ether corresponding to excess cancer risks based on the chronic oral study of Innes et al. (1969) involving male hybrid mice produced from SPF colonies (C57Bl/6 x C3H/Anf). Mice were given the maximal tolerated dose of 100 mg/kg by intubation from day 7-28, followed by dietary doses of 300 ppm for the next 76 weeks. Hepatoma incidences in the males were 8/79 for the controls and 14/16 for the treated group. U.S. EPA (1980) derived a human cancer potency

factor, q_1^* , of $1.144 \text{ (mg/kg/day)}^{-1}$ from these data assuming uniform dietary treatment for 80 weeks at 300 ppm, which gave a calculated dose of 39 mg/kg/day, and setting the exposure duration, study duration and lifespan at 80 weeks (thus obviating the dose correction for the less-than-lifespan exposure). The q_1^* , rounded to $1.1 \text{ (mg/kg/day)}^{-1}$, has been verified by U.S. EPA (1986). A reevaluation of the derivation of this potency factor (U.S. EPA, 1987a), however, concluded that the first 2 weeks of gavage dosing should be considered in calculating the animal dosage (TWA of 41.3 mg/kg/day), and the exposure duration of 79 weeks and the animal lifespan of 104 weeks should be used to make a lifespan correction. Taking these considerations into account, and using the same incidence data, U.S. EPA (1987a) estimated a human q_1^* of $2.46 \text{ (mg/kg/day)}^{-1}$, which differs by a factor of ~2 from the verified value.

Using the verified (unrounded) q_1^* of $1.144 \text{ (mg/kg/day)}^{-1}$ for bis(2-chloroethyl) ether and assuming 70 kg body weight and a daily intake of 2 L of water and 6.5 g of fish and shellfish with a BCF for bis(2-chloroethyl) ether of 6.9, the criteria for bis(2-chloroethyl) ether in ambient water remain essentially as calculated in the original AWQCD (U.S. EPA, 1980):

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria ($\mu\text{g/L}$)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 L of drinking water and consumption of 6.5 g of fish and shellfish	0	0.003	0.030	0.30	3.0
Consumption of fish and shellfish only	0	0.136	1.36	13.6	136

U.S. EPA (1980) derived criterion as a guideline for bis(2-chloro-1-methylethyl) ether using an unpublished NCI (1978) study, pending the outcome of NTP retesting. A LOAEL of 10 mg/kg/day was determined for an increased incidence of centrilobular necrosis of the liver in mice, which was not seen in the high-dose group. Reflecting the concern for potential carcinogenicity and lack of a positive dose-response relationship, an uncertainty factor of 1000 was assigned together with an additional uncertainty factor of 10 for the use of a LOAEL instead of a NOAEL. An ADI of 70 $\mu\text{g}/\text{day}$ for humans was derived. An interim ambient water quality criterion of 34.7 $\mu\text{g}/\text{l}$ was derived assuming consumption of 2 l of water and 6.5 g of fish and shellfish with a BCF for bis(2-chloro-1-methylethyl) ether of 2.47. The criterion for the consumption of fish and shellfish only was 4.36 mg/l.

Data from an NTP (1982) gavage study demonstrates the carcinogenicity of technical bis(2-chloro-1-methylethyl) ether in mice, it is therefore more appropriate to derive carcinogenicity-based ambient water quality criteria. A recent Agency assessment (U.S. EPA, 1987a) derived a slope factor (q_1^*) of $6.97 \times 10^{-2} (\text{mg}/\text{kg}/\text{day})^{-1}$ based on the dose-response data for hepatocellular adenoma and carcinoma in male mice in the NTP (1982) study.

Using the oral human carcinogenicity potency factor of $6.97 \times 10^{-2} (\text{mg}/\text{kg}/\text{day})^{-1}$ for technical bis(2-chloro-1-methylethyl) ether (U.S. EPA, 1987a) and assuming 70 kg body weight and a daily intake of 2 l of water and 6.5 g of fish and shellfish with a BCF for bis(2-chloro-1-methylethyl)

ether of 2.47, the criteria for technical bis(2-chloro-1-methylethyl) ether in ambient water are as follows:

Exposure Assumptions (per day)	<u>Risk Levels and Corresponding Criteria ($\mu\text{g}/\text{L}$)</u>				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 L of drinking water and consumption of 6.5 g of fish and shellfish	0	0.050	0.498	4.98	49.8
Consumption of fish and shellfish only	0	6.26	62.6	626	6260

EXISTING STANDARDS AND CRITERIA

ACGIH (1987) classifies chloromethyl methyl ether in category A2 - suspected human carcinogen - and has not adopted a TLV for this compound.

ACGIH (1987) classifies bis(chloromethyl) ether under category A1 - confirmed human carcinogen - and has adopted a TLV-TWA of 0.001 ppm or 0.005 mg/m³.

The U.S. EPA (1988a) has verified an inhalation slope factor of 2.2×10^2 for the carcinogenicity of bis(chloromethyl) ether.

The ACGIH (1987) TLV-TWA and STEL (with a skin notation) for bis(chloroethyl) ether are 5 ppm (30 mg/m³) and 10 ppm (60 mg/m³), respectively. OSHA (1985) lists the PEL for bis(chloroethyl) ether as 15 ppm (90 mg/m³) with a skin notation.

An inhalation slope factor for the carcinogenicity of bis(chloroethyl) ether of $1.1 \text{ (mg/kg/day)}^{-1}$ has been verified and is available on IRIS (U.S. EPA, 1986). An RQ of 10 pounds has been proposed for bis(chloroethyl) ether based on its potential carcinogenicity (U.S. EPA, 1988b).

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